Phthalate Ester-Induced Malformations are Associated with Changes in Gene Expression and Steroid Hormone Production in the Fetal Rat Testis During Sexual Differentiation

Authors: Vickie S. Wilson, Christy Lambright, Johnathan Furr, Joseph Ostby, Carmen Wood, Gary Held, L. Earl Gray, Jr.

Keywords: Phthalate, DEHP, fetal testis, gene expression, insl3

Recently, concern has arisen over the apparent increase in male reproductive health problems and the potential role of endocrine disrupting chemicals (EDCs) in the etiology of these conditions. Declining sperm counts, altered sex ratios, and increased incidences of hypospadias, cryptorchidism and testicular cancer all have been reported. Since only a small percentage of these lesions can be linked directly to known genetic defects, developmental exposure to man-made chemicals has been implicated in the increases in these reproductive malformations. The phthalate esters (PE) are high production volume, ubiquitous environmental chemicals that induce male rat reproductive tract malformations when administered during sexual differentiation. To date in studies with antiandrogenic chemicals, PE are the only class that produces agenesis of the gubernacular ligments. In the current study, we hypothesize that phthalate-induced lesions of the gubernacular ligaments, which are critical for testis descent, likely result from an inhibition of insulin-like hormone 3 (insl3) gene expression, a recently discovered peptide hormone synthesized by fetal Leydig cells. Three phthalates, di-n-ethylhexyl phthalate (DEHP), dibutyl phthalate (DBP) and benzyl butyl phthalate (BBP), were administered orally to the dam on gestation day (GD) 14 through 18 and the fetal testes were examined on GD18 for effects on steroid hormone production and insl3 gene expression. All three PE significantly reduced both *ex vivo* testosterone production and insl3 gene expression when quantified by real-time rtPCR. The results of this study provide the first demonstration of PE-induced alteration of insl3 mRNA in the fetal male rat testis. It also provides an important link between a chemical-induced malformation and a specific alteration in gene expression in the fetal testis. Potentially, alterations in fetal testosterone production and insl3 gene expression could be validated as a biomarker of effect in the fetus of phthalate-ester exposure.

Contact information: Vickie S. Wilson
Research Biologist
ORD, NHEERL, RTD
919-541-3559
wilson.vickie@epa.gov